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d his

     (FILE 'HOME' ENTERED AT 15:25:52 ON 14 AUG 2003)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE' ENTERED AT 15:26:06 ON 14 AUG 2003
L1             1 S (MARTINOL)
L2           267 S (MARINOL)
L3            42 S L2 AND (WEIGHT LOSS OR GAIN)
L4            26 S L3 NOT PY>1998
L5            21 DUP REM L4 (5 DUPLICATES REMOVED)
L6         53093 S (SYMPATHETIC NERVOUS SYSTEM)
L7             0 S L2 AND L6
L8            22 S L6 AND (CANNABINOID)
L9            16 DUP REM L8 (6 DUPLICATES REMOVED)
L10           50 S L2 AND CANNABINOID
L11            4 S L10 AND WEIGHT LOSS

=>
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FILE 'MEDLINE' ENTERED AT 15:26:06 ON 14 AUG 2003

FILE 'CAPLUS' ENTERED AT 15:26:06 ON 14 AUG 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'BIOSIS' ENTERED AT 15:26:06 ON 14 AUG 2003

FILE 'EMBASE' ENTERED AT 15:26:06 ON 14 AUG 2003


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=> s (martinol)
L1            1 (MARTINOL)

=> s (marinol)
L2          267 (MARINOL)

=> s l2 and (weight loss or gain)
L3           42 L2 AND (WEIGHT LOSS OR GAIN)

=> s l3 not py>1998
L4           26 L3 NOT PY>1998

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5            21 DUP REM L4 (5 DUPLICATES REMOVED)

=> d 1-10 bib ab

L5   ANSWER 1 OF 21     MEDLINE on STN                    DUPLICATE 1
AN   1998355109     MEDLINE
DN   98355109   PubMed ID: 9692381
TI   Abuse potential of dronabinol (Marinol).
AU   Calhoun S R; Galloway G P; Smith D E
CS   Haight Ashbury Free Clinics, Inc., San Francisco, California 94117, USA.
SO   JOURNAL OF PSYCHOACTIVE DRUGS, (1998 Apr-Jun) 30 (2) 187-96.
     Journal code: 8113536. ISSN: 0279-1072.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   199810
ED   Entered STN: 19981021
     Last Updated on STN: 19981021
     Entered Medline: 19981015
AB   Dronabinol is an oral form of delta-9-tetrahydrocannabinol indicated for
     treatment of anorexia associated with weight loss in
     individuals with AIDS, and nausea and vomiting associated with cancer
     chemotherapy. The authors reviewed the literature and conducted surveys
     and interviews among addiction medicine specialists, oncologists,
     researchers in cancer and HIV treatment, and law enforcement personnel to
     determine the abuse liability of dronabinol. There is no evidence of
     abuse or diversion of dronabinol. Available prescription tracking data
     indicates that use remains within the therapeutic dosage range over time.
     Healthcare professionals have detected no indication of "scrip-chasing" or
     "doctor-shopping" among the patients for whom they have prescribed
     dronabinol. Cannabis-dependent populations, such as those treated in our
     Clinic and seen by the addiction medicine specialists we interviewed, have
     demonstrated no interest in abuse of dronabinol. There is no street
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market for dronabinol, and no evidence of any diversion of dronabinol for sale as a street drug. Furthermore, dronabinol does not provide effects that are considered desirable in a drug of abuse. The onset of action is slow and gradual, it is at most only weakly reinforcing, and the overwhelming majority of reports of users indicate that its effects are dysphoric and unappealing. This profile of effects gives dronabinol a very low abuse potential.

L5 ANSWER 2 OF 21 MEDLINE on STN DUPLICATE 2
AN 1998355106 MEDLINE
DN 98355106 PubMed ID: 9692378
TI Medical marijuana: tribulations and trials.
AU Abrams D I
CS AIDS Program, San Francisco General Hospital, and University of California, San Francisco 94110, USA.
SO JOURNAL OF PSYCHOACTIVE DRUGS, (1998 Apr-Jun) 30 (2) 163-9.
Journal code: 8113536. ISSN: 0279-1072.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199810
ED Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981015
AB Widespread use of smoked marijuana in the San Francisco Bay Area as a treatment for HIV-related anorexia and **weight loss**, as well as nausea related to prescribed therapy, prompted the design of a clinical trial to evaluate the safety and effectiveness of this controlled substance. The Community Consortium--the Bay Area's community-based HIV clinical trials organization--designed a first pilot evaluation of smoked marijuana compared to oral tetrahydrocannabinol (THC, synthesized as dronabinol or **Marinol**) in 1993. A legal source of marijuana could not be identified. Two subsequent applications to the National Institutes of Health were submitted in 1996 and 1997. During the intervening period, increasing numbers of people with HIV infection were obtaining marijuana for "medicinal use" from local Cannabis Buyer's Clubs. In November 1996, California voters endorsed the medical use of marijuana by approving Proposition 215. The federal government's attempt to oppose the voters' mandate led to public outrage. Organized medicine demanded more studies into marijuana's potential use as medicine. The consortium's 1997 proposal to evaluate the potential interaction between THC and widely-prescribed protease inhibitors was positively received. Funding and study-required marijuana cigarettes have been obtained from the National Institute of Drug Abuse, and the first subjects are being enrolled in the trial. When politically sensitive research proposals include sound science, they can prevail if investigators are willing to persist.

L5 ANSWER 3 OF 21 MEDLINE on STN
AN 2001281831 MEDLINE
DN 98703576 PubMed ID: 11365223
TI Stimulating your appetite.
AU Whitfield L
SO POSITIVELY AWARE, (1998 Mar-Apr) 9 (2) 27.
Journal code: 9413754. ISSN: 1523-2883.
CY United States
DT (NEWSPAPER ARTICLE)
LA English
FS AIDS
EM 199806
ED Entered STN: 20010529

Last Updated on STN: 20020222
Entered Medline: 19980626

AB A number of legal and illegal drugs can help stimulate appetite and are used for people with HIV to prevent wasting. Stimulating hunger is important because lower calorie intake and poor absorption of nutrients are associated with wasting. The uses and potential drawbacks of marijuana, thalidomide (Synovir), **Marinol**, and Megace are described.

L5 ANSWER 4 OF 21 MEDLINE on STN
AN 2001283161 MEDLINE
DN 20700418 PubMed ID: 11366553
TI Products to safely increase lean muscle mass.
AU Anonymous
SO Posit Health News, (1998 Fall) (No 17) 26.
Journal code: 9890538.
CY United States
DT (NEWSPAPER ARTICLE)
LA English
FS AIDS
EM 200005
ED Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 20000503

AB Pharmaceutical companies are promoting injectable HGH or rHGH to promote the **gain** of muscle mass in persons with AIDS. Side effects can include high triglycerides, thyroid dysfunction, and increased tumor growth. A possible alternative is a Homeopathic HGH produced by Biomed Comm. Contact information for Biomed Comm is provided. **Marinol** , which contains THC, the active ingredient in marijuana, also promotes appetite and an increase in body mass. Immunocal, Optimune, and Designer Protein also appear effective in increasing lean muscle mass. Whole lemon olive oil drink is also discussed.

L5 ANSWER 5 OF 21 MEDLINE on STN
AN 2001280819 MEDLINE
DN 97702502 PubMed ID: 11364211
TI HIV-related **weight loss**.
AU Anonymous
SO PI PERSPECTIVE, (1997 Mar) (No 21) 16.
Journal code: 9102818. ISSN: 1058-7454.
CY United States
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
(NEWSPAPER ARTICLE)
LA English
FS AIDS
EM 199704
ED Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 19970416

AB Data from a recent study of the testosterone patch do not support its use for treating HIV-related **weight loss**. Testosterone as a therapy may require higher doses than the body normally produces. Currently, the only approved therapies are megestrol (Megace), dronabinol (**Marinol**), and recombinant human growth hormone (Serostim). More encouraging results come from data on thalidomide. Specifics will be forthcoming. Interested parties can call the Project Inform Treatment Hotline for updates.

L5 ANSWER 6 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 97009547 EMBASE

DN 1997009547
TI Study finds Dronabinol promising in Alzheimer disease.
SO Journal of Pharmacy Technology, (1996) 12/6 (294).
ISSN: 8755-1225 CODEN: JPTEEB
CY United States
DT Journal; Note
FS 032 Psychiatry
037 Drug Literature Index
LA English

L5 ANSWER 7 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 96088865 EMBASE
DN 1996088865
TI Megestrol acetate in patients with AIDS-related cachexia.
AU Bell S.J.; Hestnes J.C.; Wanke C.; Forse R.A.
SO Journal of Parenteral and Enteral Nutrition, (1996) 20/2 (165-166).
ISSN: 0148-6071 CODEN: JPENDU
CY United States
DT Journal; Note
FS 006 Internal Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
LA English

L5 ANSWER 8 OF 21 MEDLINE on STN
AN 2001280151 MEDLINE
DN 96701625 PubMed ID: 11363543
TI Experts leery of new oral testosterone treatment.
AU Anonymous
SO AIDS ALERT, (1996 Jun) 11 (6) 66-7.
Journal code: 8608900. ISSN: 0887-0292.
CY United States
DT (NEWSPAPER ARTICLE)
LA English
FS AIDS
EM 199607
ED Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 19960702
AB Controversy exists about the use of a new oral testosterone treatment, oxandralone (Oxandrin), manufactured by Bio-Technology General of Iselin, NJ. The drug was approved through the Food and Drug Administration's investigational new drugs (IND) procedure for promoting weight **gain** in HIV-positive individuals. Oxandralone, approved in the 1960s for disorders affecting growth in children, has been shown to have more anabolic activity and fewer masculinizing effects than other testosterone drugs, according to the company literature. However, experts in wasting syndrome are not prescribing the drug for their patients until larger efficacy studies are conducted. Some experts are prescribing the drug for patients identified with low levels of testosterone--research shows that about 20 percent of HIV-positive men have low testosterone levels. Kaposi's sarcoma (KS) may be an adverse effect of the testosterone supplement. Several case reports show that high doses of testosterone can suppress the biological mechanisms that help control KS lesions. Currently, the most effective treatment for wasting is human growth hormone therapy. However, the cost of the treatment, $1,000 per week, is too high for many. Two other drugs approved for the treatment of wasting are **Marinol** and Megace. In addition, progressive resistance exercise is effective in HIV-positive patients, even with advanced HIV disease and AIDS.

L5 ANSWER 9 OF 21 MEDLINE on STN

AN 2001280154 MEDLINE
DN 96701628 PubMed ID: 11363546
TI Testosterone replacement, weight lifting help wasting.
AU Anonymous
SO AIDS ALERT, (1996 Jun) 11 (6) suppl 1-2.
Journal code: 8608900. ISSN: 0887-0292.
CY United States
DT (NEWSPAPER ARTICLE)
LA English
FS AIDS
EM 199607
ED Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 19960702
AB Many individuals with AIDS will experience HIV wasting syndrome at some time in their disease progression. However, a number of new treatments, including anabolic steroids and a regular regimen of weight lifting, are providing benefits to those who experience this condition. .Because wasting is difficult to stop once it has started, preventing or delaying the condition is imperative. Preventive measures include eating well, avoiding infections, and exercising. Treatments and interventions for wasting include nutritional supplements, appetite stimulants, anabolic steroids such as testosterone replacement, human growth hormone therapy, and weight lifting. However, the most effective human growth hormone therapy is probably expensive. Anabolic steroids can be valuable for the 20 percent of HIV-positive males who have below-normal levels of testosterone. Two appetite stimulants approved for use in AIDS patients with **weight loss** are megestrol acetate (Megace) and dronabinol (**Marinol**). Weight lifting is a natural way to **gain** lean body mass and muscle and has been shown to be effective in people who have advanced to a diagnosis of AIDS. Seven tips for fighting **weight loss** are included.

L5 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 3
AN 1995:900671 CAPLUS
DN 123:338204
TI Effects of dietary casein and fish oil on plasma cholesterol levels in young chicks
AU Choi, I. S.; Chee, K. M.
CS Dep. Animal Sci., Korea Univ., Seoul, 136-701, S. Korea
SO Han'guk Ch'uksan Hakhoechi (1995), 37(2), 127-35
CODEN: HGCHAG; ISSN: 0367-5807
PB Korean Society of Animal Sciences
DT Journal
LA Korean
AB This study was designed to investigate any possible interactions between the mechanisms for the hypercholesterolemic effect of dietary casein and the hypocholesterolemic effect of dietary fish oil(**Marinol** contg. EPA 24.8% and DHA 10.1%) in young chicks. Two feeding trials were conducted using a strain of Single Comb White Leghorn male chicks of about one-week old. The diets in Exp. 1 and 2 were fed ad libitum for 28 and 14 days, resp. Consumption of casein, compared to that of soy protein, led to a remarkable redn. in feed intake and body wt. **gain**. However, no significant differences were obsd. between performances of chicks fed the diets contg. fish oil or corn oil. Consumption of the casein diet caused a significant increase in total plasma cholesterol levels, and that was primarily due to the increased level of lipoprotein cholesterol rather than high d. lipoprotein cholesterol. In Exp. 2 where casein was the only protein source, ingestion of the diets with added cholesterol led to a severe hypercholesterolemia mainly because of the increase in the level of plasma low d. lipoprotein cholesterol. This response was most remarkable in the chicks fed the corn oil diets with

added cholesterol. An interesting observation was that chicks fed the fish oil diet appeared to have significantly lower plasma cholesterol levels compared to those of the corn oil group(P<0.05). However, fish oil intake was not quite effective in preventing hypercholesterolemia in chicks fed the diet without supplemental cholesterol. These results seem to suggest that the control mechanisms for plasma cholesterol levels by fish oil and casein might not be interrelated.

=> d 11-21 bib ab

L5 ANSWER 11 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 95100005 EMBASE
DN 1995100005
TI Dronabinol as a treatment for anorexia associated with **weight loss** in patients with AIDS.
AU Beal J.E.; Olson R.; Laubenstein L.; Morales J.O.; Bellman P.; Yangco B.; Lefkowitz L.; Plasse T.F.; Shepard K.V.
CS PO Box 16532,Columbus, OH 43216, United States
SO Journal of Pain and Symptom Management, (1995) 10/2 (89-97).
ISSN: 0885-3924 CODEN: JPSMEU
CY United States
DT Journal; Article
FS 006 Internal Medicine
008 Neurology and Neurosurgery
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The effects of dronabinol on appetite and weight were evaluated in 139 patients with AIDS-related anorexia and .gtoreq.2.3 kg **weight loss** in a multi- institutional study. Patients were randomized to receive 2.5 mg dronabinol twice daily or placebo. Patients rated appetite, mood, and nausea by using a 100-mm visual analogue scale 3 days weekly. Efficacy was evaluable in 88 patients. Dronabinol was associated with increased appetite above baseline (38% vs 8% for placebo, P = 0.015), improvement in mood (10% vs -2%, P = 0.06), and decreased nausea (20% vs 7%; P = 0.05). Weight was stable in dronabinol patients, while placebo recipients had a mean loss of 0.4 kg (P = 0.14). Of the dronabinol patients, 22% gained .gtoreq.2 kg, compared with 10.5% of placebo recipients (P = 0.11). Side effects were mostly mild to moderate in severity (euphoria, dizziness, thinking abnormalities); there was no difference in discontinued therapy between dronabinol (8.3%) and placebo (4.5%) recipients. Dronabinol was found to be safe and effective for anorexia associated with **weight loss** in patients with AIDS.

L5 ANSWER 12 OF 21 MEDLINE on STN
AN 2001278804 MEDLINE
DN 95700087 PubMed ID: 11362199
TI Pharmacologic agents used for nutritional disorders of HIV/AIDS.
AU Rosen G H
CS University of Maryland, School of Medicine, College Park, MD 20742.
SO JOURNAL OF THE PHYSICIANS ASSOCIATION FOR AIDS CARE, (1995 Jan) 2 (1) 30-2. Ref: 17
Journal code: 9431848. ISSN: 1074-2395.
CY United States
DT (NEWSPAPER ARTICLE)
General Review; (REVIEW)
LA English
FS AIDS

EM 199503
ED Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 19950306
AB **Weight loss** in the HIV patient appears to result from the interplay of poor nutritional intake, altered metabolism, and malabsorption. Rapid **weight loss**, defined as greater than 4 kg in four months or less, is associated with non-gastrointestinal secondary infection; and slower **weight loss** is typically associated with diarrheal disorders, malabsorption and villous atrophy. Non-infectious causes of HIV-associated diarrhea may include hyperosmolar tubal feedings, antibiotics, magnesium-containing antacids and supplements, Vitamin C, or sorbitol-containing liquid medications. Antidiarrheal agents fall into three categories: antimotility agents, agents acting directly in the intestinal lumen, and hormonal agents such as octreotide. In one study, 41 percent of the subjects experienced a reduction in diarrhea when treated with octreotide. Nutritional deficits may be associated with painful symptoms of opportunistic infections, side effects of medications, lifestyle issues or psychological issues related to drug treatment. Such deficits can be treated with nutritional supplements, megestrol acetate (Megace), dronabinol (**Marinol**) and testosterone therapy. One study compared Advéra, a recently-released peptide-based nutritional supplement, with a standard formulation, Ensure. It was found to result in better maintenance of body weight with significantly fewer hospitalizations. Recombinant human erythropoietin has been shown to reduce the number of transfusions required in patients receiving zidovudine with low endogenous erythropoietin levels (<500 IU/L). Where it fails to increase the serum hematocrit, iron deficiency is often present. Supplemental iron, given orally as a tablet or liquid, or intravenously as iron dextran, can help resolve this problem.

L5 ANSWER 13 OF 21 MEDLINE on STN
AN 2001278801 MEDLINE
DN 95700084 PubMed ID: 11362196
TI AIDS-associated anorexia.
AU Beal J; Flynn N
CS University of California Davis, Medical Center, Internal Medicine Department, Division of General Medicine, AIDS and Related Disorders Clinic, Sacramento, CA 95817.
SO JOURNAL OF THE PHYSICIANS ASSOCIATION FOR AIDS CARE, (1995 Jan) 2 (1) 19-22. Ref: 15
Journal code: 9431848. ISSN: 1074-2395.
CY United States
DT (CLINICAL TRIAL)
(NEWSPAPER ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
General Review; (REVIEW)
LA English
FS AIDS
EM 199503
ED Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 19950306
AB The pathogenesis of AIDS-associated anorexia involves any one or a combination of several factors, including malnutrition and nutrient abnormalities, gastrointestinal dysfunction, metabolic dysfunctions, neuropsychiatric disturbances, economic and sociocultural factors, and anorexigenic medications. Appropriate management of anorexia is multidisciplinary, involving pharmacologic assessment, neuropsychiatric evaluation, and appetite stimulants. Two pharmacologic agents, the cannabinoid dronabinol (**Marinol**) and the synthetic progesterone megestrol acetate (Megace), are approved by the FDA for use as appetite

stimulants. Corticosteroid replacement is approved to reverse anorexia and **weight loss** associated with adrenal insufficiency. The use of androgen replacement or growth hormone in the treatment of anorexia and **weight loss** is currently investigational but shows promise. Dronabinol has been studied in a double-blind appetite stimulation study run in 18 centers. The six-week study focused on appetite stimulation and weight **gain** as end points in patients with AIDS-related **weight loss**. Results are summarized, and considerations that must be addressed by the administering clinician are presented.

L5 ANSWER 14 OF 21 MEDLINE on STN
AN 2001279023 MEDLINE
DN 95700453 PubMed ID: 11362415
TI Other therapies for wasting.
AU Smart T
SO GMHC TREATMENT ISSUES, (1995 May) 9 (5) 7-8, 12.
Journal code: 9509489. ISSN: 1077-1824.
CY United States
DT (NEWSPAPER ARTICLE)
LA English
FS AIDS
EM 199507
ED Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 19950703
AB Individuals with wasting syndrome lose muscle or lean body mass rather than body fat. Several possible alternatives to the approved drugs for AIDS-related wasting are discussed. Ketotifen, an antihistamine approved in Europe, is a TNF inhibitor. Anabolic steroids are testosterone derivatives designed to increase strength and muscle. Although there are anecdotal reports of success with these steroids, their long-term safety and efficacy have yet to be established in placebo-controlled studies. An ongoing study at Mt. Sinai shows a statistically significant effect on lean body mass in the first twelve men to complete the study. Dehydroepiandrosterone (DHEA) is a hormone produced by the adrenal gland. Although its role in the body is poorly understood; it may have immunologic effects, and appears to influence metabolism. There have been no studies of DHEA's effect on weight or body composition in people with AIDS-related wasting. A study combining ketotifen and oxymetholone, the oral anabolic steroid, was presented at the Ninth International AIDS Conference. Preliminary data from a study combining ketotifen and oxymetholone showed that 18 out of 22 patients gained an average of 11.4 pounds after treatment of an average of 3.9 weeks. Finally, a trial of smoked marijuana versus the oral drug **marinol** for AIDS-related wasting syndrome may be canceled. The Drug Enforcement Administration (DEA) and the National Institute of Drug Abuse (NIDA) rejected the Community Consortium of San Francisco's proposal to obtain officially sanctioned cannabis.

L5 ANSWER 15 OF 21 MEDLINE on STN
AN 2001279223 MEDLINE
DN 96700655 PubMed ID: 11362615
TI Wasting syndrome--affordable treatments.
AU James J S
SO AIDS TREATMENT NEWS, (1995 Jul 7) (no 226) 6-7.
Journal code: 8809835. ISSN: 1052-4207.
CY United States
DT (NEWSPAPER ARTICLE)
LA English
FS AIDS
EM 199509

ED Entered STN: 20010529
Last Updated on STN: 20020222
Entered Medline: 19950912

AB Inexpensive potential treatments are available for wasting syndrome in AIDS, and early experience suggests that most patients can be successfully treated by using one or another of them. This may mean that only a few patients will need expensive treatments, such as human growth hormone or total parenteral nutrition (TPN), which cost about $1000 per week or more. Testosterone enanthate, when used with an appropriate exercise program, is an affordable treatment for AIDS-related **weight loss**.
Several leading AIDS physicians are using testosterone enanthate, in some cases with nandrolone, an anabolic steroid, with some success. Ketotifen, an affordable possibility for treating wasting syndrome, is believed to be a safe drug. Widely used in Europe for asthma and allergies, lack of research for AIDS-related wasting is its drawback. Thalidomide is available under a special, tightly controlled, underground compassionate access program through two buyers' clubs. Thalidomide may cause birth defects, and larger doses can cause neuropathy or other adverse effects. Two FDA-approved treatments for AIDS-related wasting, megestrol acetate (Megace) and dronabinol (**Marinol**), are expensive and there is controversy as to how effective they are for increasing lean body mass.

L5 ANSWER 16 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 93075292 EMBASE
DN 1993075292
TI Dronabinol approved for use in anorexia associated with **weight loss** in patients with AIDS.
AU Nightingale S.L.
CS Office of Health Affairs, FDA, Parklawn Bldg, 5600 Fishers Ln,Rockville, MD 20857, United States
SO Journal of the American Medical Association, (1993) 269/11 (1361).
ISSN: 0098-7484 CODEN: JAMAAP
CY United States
DT Journal; Note
FS 006 Internal Medicine
037 Drug Literature Index
LA English

L5 ANSWER 17 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 93225677 EMBASE
DN 1993225677
TI Effect of dronabinol on nutritional status in HIV infection.
AU Struwe M.; Kaempfer S.H.; Geiger C.J.; Pavia A.T.; Plasse T.F.; Shepard K.V.; Ries K.; Evans T.G.; Guzman W.M.; Laplante S.
CS Roxane Laboratories, P.O. Box 16532,Columbus, OH 43216, United States
SO Annals of Pharmacotherapy, (1993) 27/7-8 (827-831).
ISSN: 1060-0280 CODEN: APHRER
CY United States
DT Journal; Article
FS 004 Microbiology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English; Spanish; French
AB OBJECTIVE: To examine the effect of dronabinol (delta-9-tetrahydrocannabinol) on appetite and nutritional status in patients with symptomatic HIV infection and **weight loss**. DESIGN:
Double-blind, randomized, placebo-controlled, crossover trial with two five-week treatment periods separated by a two-week washout period. Patients received dronabinol 5 mg twice daily before meals or placebo.

SETTING: A university-based HIV/AIDS clinic and a large infectious disease private practice largely devoted to care of patients with HIV. PARTICIPANTS: Twelve HIV-infected patients who had had at least a 2.25-kg **weight loss** participated in the study. Five patients completed the protocol, and seven withdrew (two because of drug intolerance, two because of disease progression, two because of noncompliance, and one because of experimental antiretroviral therapy). MAIN OUTCOME MEASURES: Main outcome measures included caloric intake, weight, percent body fat, serum prealbumin, and symptom distress. RESULTS: During dronabinol treatment, subjects experienced increased percent body fat (one percent, p=0.04); decreased symptom distress (p=0.04); and trends toward weight **gain** (0.5 kg, p=0.13), increased prealbumin (29.0 mg/L, p=0.11), and improved appetite score (p=0.14). CONCLUSIONS: In a selected group of HIV-infected patients with **weight loss** , short-term treatment with dronabinol may result in improvement in nutritional status and symptom distress.

L5 ANSWER 18 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1992:493745 BIOSIS
DN BR43:102945
TI RANDOMIZED STUDY OF DRONABINOL IN HIV RELATED **WEIGHT LOSS.**
AU STRUWE M; KAEMPFER S H; PAVIA A T; GEIGER C J; SHEPARD K V; PLASSE T F; EVANS T
CS 50 NORTH MEDICAL DRIVE, ROOM B322, SALT LAKE CITY, UTAH 84132.
SO VIII INTERNATIONAL CONFERENCE ON AIDS AND THE III STD WORLD CONGRESS. PUBLISHED ABSTRACTS SUBMITTED TO THE VIII INTERNATIONAL CONFERENCE ON AIDS AND THE III STD WORLD CONGRESS; HARVARD-AMSTERDAM CONFERENCE, AMSTERDAM, NETHERLANDS, JULY 19-24, 1992. 220P. VIII INTERNATIONAL CONGRESS AND THE III STD WORLD CONGRESS: AMSTERDAM, NETHERLANDS. PAPER. (1992) 0 (0), 137.
DT Conference
FS BR; OLD
LA English

L5 ANSWER 19 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 92018145 EMBASE
DN 1992018145
TI Recent clinical experience with dronabinol.
AU Plasse T.F.; Gorter R.W.; Krasnow S.H.; Lane M.; Shepard K.V.; Wadleigh R.G.
CS UNIMED, Inc., 35 Columbia Road,Somerville, NJ 08876-3587, United States
SO Pharmacology Biochemistry and Behavior, (1991) 40/3 (695-700). ISSN: 0091-3057 CODEN: PBBHAU
CY United States
DT Journal; Conference Article
FS 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Dronabinol, .DELTA.-9-tetrahydrocannabinol in sesame oil, has been used for several years as an antiemetic for patients receiving cancer chemotherapy. In combination studies with prochlorperazine, enhancement of efficacy, as measured by duration of episodes of nausea and vomiting and by severity of nausea, has been found. The incidence of psychotropic effects from dronabinol appears to be decreased by concomitant administration of prochlorperazine. In open pilot studies, dronabinol caused weight **gain** in seven of ten patients with symptomatic HIV infection. In both HIV and cancer patients, dronabinol improved appetite at a dose which was well tolerated for chronic administration.

L5 ANSWER 20 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 91332539 EMBASE
DN 1991332539
TI Phase II clinical results reported on **Marinol**.RTM..
SO AIDS Patient Care, (1991) 5/5 (265).
ISSN: 0893-5068 CODEN: APACEF
CY United States
DT Journal; Note
FS 017 Public Health, Social Medicine and Epidemiology
047 Virology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English

L5 ANSWER 21 OF 21 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 91109957 EMBASE
DN 1991109957
TI Nutritional support of the medical oncology patient.
AU Chlebowski R.T.
CS Division of Medical Oncology, Harbor-UCLA Medical Center, 1000 W. Carson Street,Torrance, CA 90509, United States
SO Hematology/Oncology Clinics of North America, (1991) 5/1 (147-160).
ISSN: 0889-8588 CODEN: HCNAEQ
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
AB **Weight loss** in cancer patients is generally prognostic of decreased survival. Enteral and total parenteral nutrition has failed to improve cancer patient outcome. Pharmacologic approaches to nutritional support in this context include cyproheptadine, corticosteroids, progestational agents, dronabinol, metoclopramide, nandrolone decanoate, insulin, and hydrazine sulfate.

=> d his

(FILE 'HOME' ENTERED AT 15:25:52 ON 14 AUG 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE' ENTERED AT 15:26:06 ON 14 AUG 2003
L1 1 S (MARTINOL)
L2 267 S (MARINOL)
L3 42 S L2 AND (WEIGHT LOSS OR GAIN)
L4 26 S L3 NOT PY>1998
L5 21 DUP REM L4 (5 DUPLICATES REMOVED)

=> s (sympathetic nervous system)
L6 53093 (SYMPATHETIC NERVOUS SYSTEM)

=> s l2 and l6
L7 0 L2 AND L6

=> s l6 and (cannabinoid)
L8 22 L6 AND (CANNABINOID)

=> DUP REM L8
PROCESSING COMPLETED FOR L8
L9 16 DUP REM L8 (6 DUPLICATES REMOVED)

=> D 1-10 BIB AB

L9 ANSWER 1 OF 16 MEDLINE on STN
AN 2003161745 MEDLINE
DN 22565425 PubMed ID: 12521935
TI Microinjection of a **cannabinoid** receptor antagonist into the NTS increases baroreflex duration in dogs.
AU Rademacher David J; Patel Sachin; Hopp Francis A; Dean Caron; Hillard Cecilia J; Seagard Jeanne L
CS Department of Pharmacology and Toxicology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226-0509, USA.
NC DA 09155 (NIDA)
SO AMERICAN JOURNAL OF PHYSIOLOGY. HEART AND CIRCULATORY PHYSIOLOGY, (2003 May) 284 (5) H1570-6.
Journal code: 100901228. ISSN: 0363-6135.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Space Life Sciences
EM 200305
ED Entered STN: 20030408
Last Updated on STN: 20030516
Entered Medline: 20030515
AB Baroreceptor afferent fibers synapse in the nucleus tractus solitarius (NTS) of the medulla. Neuronal **cannabinoid** (CB)(1) receptors are expressed in the NTS and central administration of CB(1) receptor agonists affect blood pressure (BP) and heart rate. In addition, there is evidence that endocannabinoids are produced in the brain stem. This study examined whether changes in CB(1) receptor activity in the NTS modulated the baroreceptor reflex, contributing to changes seen in BP and heart rate. Baroreflexes were evoked in anesthetized dogs by pressure ramp stimulations of the isolated carotid sinus before and after microinjection of CB(1) receptor agonist WIN-55212-2 (1.25-1.50 pmol) or antagonist SR-141716 (2.5-3.0 pmol) into cardiovascular regions of the NTS. Microinjection of the SR-141716 did not affect baseline BP or baroreflex sensitivity. However, SR-141716 significantly prolonged the time needed to return to the baseline level of BP after the pressure ramp. Microinjection of WIN-55212-2 had no effect on the baroreflex. These data suggest that endocannabinoids can modulate the excitability of NTS neurons involved in the baroreceptor reflex, leading to modulation of baroreflex regulation.

L9 ANSWER 2 OF 16 MEDLINE on STN DUPLICATE 1
AN 2003228818 IN-PROCESS
DN 22635743 PubMed ID: 12709782
TI The peripheral **sympathetic nervous system** is the major target of cannabinoids in eliciting cardiovascular depression.
AU Niederhoffer Nathalie; Schmid Karin; Szabo Bela
CS Institut fur Experimentelle und Klinische Pharmakologie und Toxikologie, Albertstrasse 25, 79104 Freiburg i. Br., Germany..
nathalie.niederhoffer@pharmakol.uni-freiburg.de
SO NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, (2003 May) 367 (5) 434-43.
Journal code: 0326264. ISSN: 0028-1298.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20030517
Last Updated on STN: 20030708
AB Our objective was to identify the sites of interaction of cannabinoids with cardiovascular sympathetic regulation in the rat. Effects on

sympathetic tone were first determined in anaesthetised animals following i.v. administration of the drugs. Central effects were evaluated in anaesthetised rats receiving microinjections of cannabinoids into brain stem nuclei. Peripheral effects were identified in pithed rats with electrically stimulated sympathetic outflow.In anaesthetised and artificially ventilated rats, i.v. injection of the **cannabinoid** agonists WIN55212-2 and CP55940 decreased mean arterial pressure, heart rate and the plasma noradrenaline concentration. These effects were antagonized by the CB(1) **cannabinoid** receptor antagonist SR141716A. The bradycardia was abolished by the muscarinic acetylcholine receptor antagonist methylatropine. The decreases in mean arterial pressure and heart rate caused by cannabinoids in ventilated rats were much less pronounced than in spontaneously breathing rats. Microinjection of WIN55212-2 into the nucleus tractus solitarii had no effect. Microinjected into the rostral ventrolateral medulla oblongata, WIN55212-2 lowered mean arterial pressure slightly without changing other parameters. In pithed rats, WIN55212-2 inhibited the increases in mean arterial pressure, heart rate and the plasma noradrenaline concentration evoked by electrical stimulation of the sympathetic outflow.Our results show that activation of CB(1) **cannabinoid** receptors induces sympathoinhibition and enhancement of cardiac vagal tone, leading to hypotension and bradycardia. Presynaptic inhibition of noradrenaline release from terminals of postganglionic sympathetic neurons is the major component of the sympathoinhibition, but an effect in the rostral ventrolateral medulla oblongata may also contribute. The **cannabinoid**-evoked cardiovascular depression depends strongly on the respiratory state of the animals.

L9 ANSWER 3 OF 16 MEDLINE on STN
AN 2003190615 MEDLINE
DN 22595794 PubMed ID: 12709683
TI Endocannabinoids as autoregulatory signaling molecules: coupling to nitric oxide and a possible association with the relaxation response.
AU Stefano George B; Esch Tobias; Cadet Patrick; Zhu Wei; Mantione Kirk; Benson Herbert
CS The Mind/Body Medical Institute, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.. gstefano@sunynri.org
NC DA 09010 (NIDA)
H75/CCH119124 (CDC)
SO MEDICAL SCIENCE MONITOR, (2003 Apr) 9 (4) RA63-75. Ref: 105
Journal code: 9609063. ISSN: 1234-1010.
CY Poland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200308
ED Entered STN: 20030424
Last Updated on STN: 20030802
Entered Medline: 20030801
AB Endocannabinoid signaling processes are present in diverse organisms and in organisms 500 million years divergent in evolution. **Cannabinoid** receptor-1 expression (CB1), anandamide, and anandamide amidase have been found in invertebrates. Furthermore, this signaling system is coupled to constitutive nitric oxide synthase (cNOS)-derived nitric oxide (NO) release in both vertebrates and invertebrates, thereby regulating neural, immune, and vascular-like functions in these divergent organisms. In human endothelial cells from various blood vessels, CB1 immunoreactive components are present as is its coupling to anandamide-stimulated cNOS-derived NO production, which exerts

an autoregulatory role on cNOS release. The modulation of vascular diameter and vascular tone represents a crucial point of interest in these pathways, and interactions between NO and the sympathetic nerve system are of importance, i.e, norepinephrine. Here, a possible association of NO and endocannabinoid signaling with the relaxation response, a physiological counterpart of the stress response, may exist.

L9 ANSWER 4 OF 16 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
AN 2002094877 EMBASE
TI Fine tuning of sympathetic transmitter release via ionotropic and metabotropic presynaptic receptors.
AU Boehm S.; Kubista H.
CS S. Boehm, Institute of Pharmacology, University of Vienna, Waehringerstrasse 13a, A-1090 Vienna, Austria. Stefan.Boehm@univie.ac.at
SO Pharmacological Reviews, (2002) 54/1 (43-99).
Refs: 594
ISSN: 0031-6997 CODEN: PAREAQ
CY United States
DT Journal; General Review
FS 002 Physiology
030 Pharmacology
LA English
SL English
AB The release of transmitters at sympathoeffector junctions is not constant, but subject to modulation by a plethora of different mechanisms. In this respect, presynaptic receptors located on the sympathetic axon terminals are of utmost importance, because they are activated by exogenous agonists and by endogenous neurotransmitters. In the latter case, the transmitters that activate the presynaptic receptors of a nerve terminal may be released either from the very same nerve ending or from a different axon terminal, and the receptors involved are auto- and heteroreceptors, respectively. In terms of their structural and functional features, receptors of sympathetic axon terminals can be categorized as either ionotropic (transmitter-gated ion channels) or metabotropic (most commonly G protein-coupled) receptors. This review summarizes results on more than 30 different metabotropic and four different ionotropic receptors that have been found to control the amount of transmitter being released from sympathetic neurons. Each of these receptors may not only stimulate, facilitate, and reduce sympathetic transmitter release, respectively, but also interact with the functions of other receptors present on the same axonal varicosity. This provides a multitude of mechanisms that regulate the amount of sympathetic transmitter output. Accordingly, a sophisticated cross-talk within and between extra- and intracellular signals is integrated at axon terminals to adapt the strength of sympathoeffector transmission to a given situation. This will not only determine the function of the **sympathetic nervous system** in health and disease, but also therapeutic and untoward effects of drugs that bind to the presynaptic receptors in sympathetically innervated tissues.

L9 ANSWER 5 OF 16 MEDLINE on STN
AN 2001271123 MEDLINE
DN 21199608 PubMed ID: 11303075
TI Effects of cannabinoids on sympathetic and parasympathetic neuroeffector transmission in the rabbit heart.
AU Szabo B; Nordheim U; Niederhoffer N
CS Institut fur Experimentelle und Klinische Pharmakologie und Toxikologie, Albert-Ludwigs-Universitat, Freiburg, Germany.. szabo@uni-frieburg.de
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2001 May) 297 (2) 819-26.
Journal code: 0376362. ISSN: 0022-3565.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010529
Last Updated on STN: 20010529
Entered Medline: 20010521
AB Cannabinoids elicit marked cardiovascular responses. It is not clear how peripheral effects on the autonomic nervous system contribute to these responses. The aim of the present study was to characterize the peripheral actions of cannabinoids on the autonomic innervation of the heart. Experiments were carried out on pithed rabbits. In the first series of experiments, postganglionic sympathetic cardioaccelerator fibers were stimulated electrically. The synthetic **cannabinoid** receptor agonists WIN55212-2 (0.005, 0.05, 0.5, and 1.5 mg kg(-1) i.v.) and CP55940 (0.003, 0.03, 0.3, and 1 mg kg(-1) i.v.) dose dependently inhibited the electrically evoked cardioacceleration. The inhibition by WIN55212-2 (0.5 mg kg(-1) i.v.) was prevented by the CB(1) **cannabinoid** receptor antagonist SR141716A (0.5 mg kg(-1) i.v.). WIN55212-2 (0.5 mg kg(-1) i.v.) did not change the increase in heart rate evoked by injection of isoprenaline. In the second series of experiments, preganglionic vagal fibers were stimulated electrically. WIN55212-2 (0.005, 0.05, and 0.5 mg kg(-1) i.v.) and CP55940 (0.003, 0.03, and 0.3 mg kg(-1) i.v.) dose dependently inhibited the stimulation-evoked decrease in heart rate. The inhibition produced by WIN55212-2 (0.005, 0.05, and 0.5 mg kg(-1) i.v.) was antagonized by SR141716A (0.5 mg kg(-1) i.v.). The results indicate that cannabinoids, by activating CB(1) **cannabinoid** receptors, inhibit sympathetic and vagal neuroeffector transmission in the heart. The mechanism of the sympathoinhibition is probably presynaptic inhibition of noradrenaline release from postganglionic sympathetic neurons. The mechanism of the inhibition of vagal activity was not clarified: cannabinoids may have an inhibitory action on both pre- and postganglionic vagal neurons.

L9 ANSWER 6 OF 16 MEDLINE on STN
AN 2001569791 MEDLINE
DN 21530739 PubMed ID: 11676206
TI 2-Arachidonoylglycerol and anandamide oppositely modulate norepinephrine release from the rat heart sympathetic nerves.
AU Kurihara J; Nishigaki M; Suzuki S; Okubo Y; Takata Y; Nakane S; Sugiura T; Waku K; Kato H
CS Department of Pharmacology, Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa, Japan.. jun-kuri@pharm.teikyo-u.ac.jp
SO JAPANESE JOURNAL OF PHARMACOLOGY, (2001 Sep) 87 (1) 93-6.
Journal code: 2983305R. ISSN: 0021-5198.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200204
ED Entered STN: 20011029
Last Updated on STN: 20020501
Entered Medline: 20020430
AB Anandamide (10(-7) and 10(-6) M) as well as a synthetic **cannabinoid** HU210 (10(-8) to 10(-6) M) suppressed the norepinephrine release evoked by perivascular nerve stimulation (PNS) of the rat heart Langendorff's preparation. The effects of HU210 and the lower dose of anandamide were completely blocked by the **cannabinoid** CB1-receptor antagonist AM251, while that of anandamide at 10(-6) M was partly mediated by arachidonate-derived metabolites. 2-Arachidonoylglycerol (2-AG), at 10(-6) M in the presence of DFP and indomethacin, increased PNS-evoked norepinephrine release, which

was completely blocked by AM251. The present results suggest that the two endocannabinoids may oppositely participate in the CB1-receptor-mediated modulation of sympathetic norepinephrine release.

L9 ANSWER 7 OF 16 MEDLINE on STN
AN 2001017836 MEDLINE
DN 20490948 PubMed ID: 11032898
TI Electrically evoked release of [(3)H]noradrenaline from mouse cultured sympathetic neurons: release-modulating heteroreceptors.
AU Gobel I; Trendelenburg A U; Cox S L; Meyer A; Starke K
CS Pharmakologisches Institut, Freiburg im Breisgau, Germany.
SO JOURNAL OF NEUROCHEMISTRY, (2000 Nov) 75 (5) 2087-94.
Journal code: 2985190R. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20021218
Entered Medline: 20001109
AB Cultured neurons from the thoracolumbar sympathetic chain of newborn mice are known to possess release-inhibiting alpha(2)-autoreceptors. The present study was carried out in a search for release-modulating heteroreceptors on these neurons. Primary cultures were preincubated with [(3)H]noradrenaline and then superfused and stimulated by single pulses, trains of 8 pulses at 100 Hz, or trains of 36 pulses at 3 Hz. The cholinergic agonist carbachol reduced the evoked overflow of tritium. Experiments with antagonists indicated that the inhibition was mediated by M(2) muscarinic receptors. The **cannabinoid** agonist WIN 55,212-2 reduced the evoked overflow of tritium through CB(1) receptors. Prostaglandin E(2), sulprostone, and somatostatin also caused presynaptic inhibition. The inhibitory effects of carbachol, WIN 55,212-2, prostaglandin E(2), and somatostatin were abolished (at the highest concentration of WIN 55, 212-2 almost abolished) by pretreatment of the cultures with pertussis toxin (250 ng/ml). Several drugs, including the beta(2)-adrenoceptor agonist salbutamol, opioid receptor agonists, neuropeptide Y, angiotensin II, and bradykinin, failed to change the evoked overflow of tritium. These results demonstrate a distinct pattern of presynaptic inhibitory heteroreceptors, all coupled to pertussis toxin-sensitive G proteins. The lack of operation of several presynaptic receptors known to exist in adult mice in situ may be due to the age of the (newborn) donor animals or to the culture conditions.

L9 ANSWER 8 OF 16 MEDLINE on STN
AN 2000405621 MEDLINE
DN 20361988 PubMed ID: 10900251
TI Cannabinoids cause central sympathoexcitation and bradycardia in rabbits.
AU Niederhoffer N; Szabo B
CS Institut fur Pharmakologie und Toxikologie, Albert-Ludwigs-Universitat, Freiburg, Germany.
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2000 Aug) 294 (2) 707-13.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200008
ED Entered STN: 20000901
Last Updated on STN: 20021210
Entered Medline: 20000824

AB Systemically administered cannabinoids elicit marked cardiovascular effects, and the role of the central and the peripheral nervous system in these effects is not clarified. The aim of this study was to characterize the actions of cannabinoids on cardiovascular regulatory centers in conscious rabbits. A catheter for administration of drugs into the cisterna cerebellomedullaris and an electrode for recording renal sympathetic nerve activity were implanted under halothane anesthesia. Experiments were carried out later in conscious animals. Two **cannabinoid** receptor agonists were injected intracisternally: the aminoalkylindole WIN55212-2 (0.1, 1, and 10 microg kg(-1)) and the bicyclic Delta(9)-tetrahydrocannabinol analog CP55940 (0.1, 1, and 10 microg kg(-1)). WIN55212-2 and CP55940 dose dependently increased renal sympathetic nerve activity and the plasma noradrenaline concentration and also lowered the heart rate. The highest doses of WIN55212-2 and CP55940 increased blood pressure. In contrast, intracisternal injection of WIN55212-3 (0.1, 1, and 10 microg kg(-1)), an enantiomer of WIN55212-2 with very low affinity for **cannabinoid** binding sites, had no effects. The CB(1) **cannabinoid** receptor antagonist SR141716A (0.5 mg kg(-1), i.v.) attenuated the effects of intracisternally administered WIN55212-2 (0.1, 1, and 10 microg kg(-1)). The results indicate that cannabinoids, acting directly on cardiovascular regulatory centers, elicit sympathoactivation and bradycardia. These effects were likely mediated by CB(1) **cannabinoid** receptors, because they were elicited by two **cannabinoid** agonists belonging to different chemical classes (WIN55212-2 and CP55940), but not by the inactive enantiomer WIN55212-3, and because they were attenuated by the CB(1) **cannabinoid** receptor antagonist SR141716A.

L9 ANSWER 9 OF 16 MEDLINE on STN
AN 2000187356 MEDLINE
DN 20187356 PubMed ID: 10720647
TI Pharmacological characterisation of **cannabinoid** CB(1) receptors in the rat and mouse.
AU Lay L; Angus J A; Wright C E
CS Department of Pharmacology, University of Melbourne, Parkville, Victoria 3010, Australia.
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (2000 Mar 10) 391 (1-2) 151-61. Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000511
AB The role of **cannabinoid** CB(1) receptors in sympathetic neurotransmission was characterised in nerve-mediated responses of isolated right atria, vasa deferentia and small mesenteric resistance arteries using the **cannabinoid** CB(1) receptor agonists Delta(9)-tetrahydrocannabinol, CP 55,940 and anandamide and the **cannabinoid** CB(1)-selective antagonist SR 141716A. In the mouse vas deferens, the twitch response was completely inhibited by each of the putative **cannabinoid** receptor agonists with pIC(50) values of CP 55,940, 9.2+/-0.1; Delta(9)-tetrahydrocannabinol, 8.4+/-0.1; anandamide, 7.1+/-0.1. SR 141716A 10-100 nM was a competitive antagonist of all three agonists with a pK(B) value of 8.4-8.6, consistent with an interaction at the **cannabinoid** CB(1) receptor. In the rat vas deferens CP 55,940 (0.01-10 microM) inhibited the contractions to a significant extent (88.5+/-0.5% at 10 microM; pIC(50) of 7.1+/-0.1) while Delta(9)-tetrahydrocannabinol and anandamide (both up to 10 microM) were inactive. CP 55,940 exhibited low potency in rat compared with mouse vas

deferens and the rat concentration-response curve was not competitively antagonised by SR 141716A (100 nM) or SR 144528 (10 nM-10 microM), suggesting an interaction at a receptor(s) distinct from **cannabinoid** CB(1) or CB(2). Sympathetic nerve-induced tachycardia in rat and mouse atria, and rat mesenteric artery smooth muscle contractile responses to perivascular nerve stimulation, were not inhibited by Delta(9)-tetrahydrocannabinol, CP 55,940 or anandamide up to 1 microM. These data indicate that **cannabinoid** CB(1) receptor activation inhibits sympathetic neurotransmission only in the mouse vas deferens and thus point to species and regional differences in **cannabinoid** CB(1) receptor involvement in pre-synaptic inhibition of sympathetic neurotransmission and CP 55,940 may have inhibitory actions in rat vas deferens unrelated to **cannabinoid** receptor activity.

L9 ANSWER 10 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:121333 BIOSIS
DN PREV200100121333
TI Inhibition of nicotine-stimulated catecholamine release from adrenal chromaffin cells by the **cannabinoid** agonist, WIN 55,212-2.
AU Romstedt, K. J. (1); Hutchison, S. E.; Free, R. B.; McKay, D. B.
CS (1) The Ohio State University, Columbus, OH USA
SO Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-814.10. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience . ISSN: 0190-5295.
DT Conference
LA English
SL English
AB Although their physiological role is unclear, **cannabinoid** receptors have been identified in mammals and cannabinoids have been shown to inhibit norepinephrine release from peripheral sympathetic nerves in rat atria and vas deferens (Brit. J. Pharmacol. 118, 2023, 1996). The current study investigates the effects of the **cannabinoid** receptor agonist, Win 55,212-2, on catecholamine release from bovine adrenal chromaffin cells. Chromaffin cells are peripheral neuroendocrine cells which function as postganglionic effectors of the **sympathetic nervous system**. WIN 55,212-2, when used alone, has no effects on catecholamine release from cultured bovine adrenal chromaffin cells. However, when cells are treated with WIN 55,212-2, subsequent release of catecholamines stimulated by nicotine (10 muM) is inhibited. These inhibitory effects of WIN 55,212-2 were concentration-dependent (IC50 value, apprx 5 muM), rapid in onset (< 5 min) and quickly reversible after washout. nAChR binding assays demonstrated that the actions of WIN 55,212-2 do not involve inhibition of binding. WIN 55,212-2 also inhibited catecholamine release stimulated by a depolarizing concentration of KCl (IC50 value, apprx25 muM). In contrast, WIN 55,212-2 at concentrations up to 100 muM did not show significant inhibitory effects on catecholamine secretion when BaCl2 was used as the secretagogue. The mechanism of action of WIN 55,212-2 on the inhibition of adrenal catecholamine release remains to be defined. However, several possibilities exist such as WIN 55,212-2 interacting directly with K+ and/or Ca++ channels or **cannabinoid** receptors on adrenal chromaffin cells.

=> 11-16 bib ab
11-16 IS NOT A RECOGNIZED COMMAND
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"HELP COMMANDS" at an arrow prompt (=>).

=> d 11-16 bib ab

L9 ANSWER 11 OF 16 MEDLINE on STN
AN 1999174857 MEDLINE
DN 99174857 PubMed ID: 10077239
TI Effect of the **cannabinoid** receptor agonist WIN55212-2 on sympathetic cardiovascular regulation.
AU Niederhoffer N; Szabo B
CS Pharmakologisches Institut der Albert-Ludwigs-Universitat, Freiburg i. Br., Germany.
SO BRITISH JOURNAL OF PHARMACOLOGY, (1999 Jan) 126 (2) 457-66. Journal code: 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990507
AB 1. The aim of the present study was to analyse the cardiovascular actions of the synthetic CB1/CB2 **cannabinoid** receptor agonist WIN55212-2, and specifically to determine its sites of action on sympathetic cardiovascular regulation. 2. Pithed rabbits in which the sympathetic outflow was continuously stimulated electrically or which received a pressor infusion of noradrenaline were used to study peripheral prejunctional and direct vascular effects, respectively. For studying effects on brain stem cardiovascular regulatory centres, drugs were administered into the cisterna cerebellomedullaris in conscious rabbits. Overall cardiovascular effects of the **cannabinoid** were studied in conscious rabbits with intravenous drug administration. 3. In pithed rabbits in which the sympathetic outflow was continuously electrically stimulated, intravenous injection of WIN55212-2 (5, 50 and 500 microg kg(-1)) markedly reduced blood pressure, the spillover of noradrenaline into plasma and the plasma noradrenaline concentration, and these effects were antagonized by the CB1 **cannabinoid** receptor-selective antagonist SR141716A. The hypotensive and the sympathoinhibitory effect of WIN55212-2 was shared by CP55940, another mixed CB1/CB2 **cannabinoid** receptor agonist, but not by WIN55212-3, the enantiomer of WIN55212-2, which lacks affinity for **cannabinoid** binding sites. WIN55212-2 had no effect on vascular tone established by infusion of noradrenaline in pithed rabbits. 4. Intracisternal application of WIN55212-2 (0.1, 1 and 10 microg kg(-1)) in conscious rabbits increased blood pressure and the plasma noradrenaline concentration and elicited bradycardia; this latter effect was antagonized by atropine. 5. In conscious animals, intravenous injection of WIN55212-2 (5 and 50 microg kg(-1)) caused bradycardia, slight hypotension, no change in the plasma noradrenaline concentration, and an increase in renal sympathetic nerve firing. The highest dose of WIN55212-2 (500 microg kg(-1)) elicited hypotension and tachycardia, and sympathetic nerve activity and the plasma noradrenaline concentration declined. 6. The results obtained in pithed rabbits indicate that activation of CB1 **cannabinoid** receptors leads to marked peripheral prejunctional inhibition of noradrenaline release from postganglionic sympathetic axons. Intracisternal application of WIN55212-2 uncovered two effects on brain stem cardiovascular centres: sympathoexcitation and activation of cardiac vagal fibres. The highest dose of systemically administered WIN55212-2 produced central sympathoinhibition; the primary site of this action is not known.

L9 ANSWER 12 OF 16 MEDLINE on STN
AN 1999423076 MEDLINE

DN 99423076 PubMed ID: 10494885
TI Presynaptic **cannabinoid** and imidazoline receptors in the human heart and their potential relationship.
AU Molderings G J; Likungu J; Gothert M
CS Institut fur Pharmakologie and Toxikologie, Rheinische Friedrich-Wilhelms-Universitat Bonn, Germany.. molderings@uni-bonn.de
SO NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, (1999 Aug) 360 (2) 157-64. Journal code: 0326264. ISSN: 0028-1298.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991108
AB Segments of human right atrial appendages preincubated with [3H]noradrenaline and superfused with physiological salt solution containing desipramine and corticosterone were used to examine whether the cardiac sympathetic nerves are endowed with **cannabinoid** receptors and to further study pharmacological properties of presynaptic imidazoline receptors. The **cannabinoid** CB1 receptor agonists CP55,940, HU210 and anandamide inhibited evoked [3H]noradrenaline release. The inhibition by CP55,940 and anandamide was abolished by the CB1 receptor antagonists SR141716A (1 microM) and LY320135 (1 microM). Rauwolscine at the imidazoline receptor-blocking concentration of 30 microM abolished the inhibitory effect of CP55,940 and anandamide. After blockade of alpha2-adrenoceptors with 1 microM rauwolscine, the imidazoline binding site ligand S23230, which is the (-)-enantiomer of the racemic oxazoline derivative S22687, exhibited low potency in inhibiting electrically evoked [3H]noradrenaline release (pIC30%=4.96), whereas the (+)-enantiomer S23229 and the racemate S22687 were ineffective. In the presence of 30 microM rauwolscine, S23230 did not significantly inhibit evoked release. The imidazoline receptor-mediated inhibitory effect of BDF 6143 and aganodine on evoked [3H]noradrenaline release was abolished by 1 microM SR141716A and by 1 microM LY320135. The inhibitory effect of moxonidine on evoked [3H]noradrenaline release, which is exclusively mediated via activation of alpha2-autoreceptors, was not antagonized by 1 microM SR141716A. In conclusion, inhibitory **cannabinoid** CB1 receptors are present on the sympathetic axon terminals of human atrial appendages. Presynaptic imidazoline receptors share the property of other receptors in that they can be stereoselectively activated. The cross-antagonism of imidazoline receptor agonists/antagonists with CB1 receptor antagonists/agonists suggests that these receptors may have certain binding domains in common or that they interact with each other in an unknown manner.

L9 ANSWER 13 OF 16 MEDLINE on STN
AN 97439776 MEDLINE
DN 97439776 PubMed ID: 9294122
TI Production and physiological actions of anandamide in the vasculature of the rat kidney.
AU Deutsch D G; Goligorsky M S; Schmid P C; Krebsbach R J; Schmid H H; Das S K; Dey S K; Arreaza G; Thorup C; Stefano G; Moore L C
CS Department of Biochemistry & Cell Biology, State University of New York, Stony Brook, New York 11794, USA.
NC DA 06668 (NIDA)
DA 09010 (NIDA)
MH/DA 17138 (NIMH)
+
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CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
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EM 199712
ED Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971208
AB The endogenous **cannabinoid** receptor agonist anandamide is present in central and peripheral tissues. As the kidney contains both the amidase that degrades anandamide and transcripts for anandamide receptors, we characterized the molecular components of the anandamide signaling system and the vascular effects of exogenous anandamide in the kidney. We show that anandamide is present in kidney homogenates, cultured renal endothelial cells (EC), and mesangial cells; these cells also contain anandamide amidase. Reverse-transcriptase PCR shows that EC contain transcripts for **cannabinoid** type 1 (CB1) receptors, while mesangial cells have mRNA for both CB1 and CB2 receptors. EC exhibit specific, high-affinity binding of anandamide (Kd = 27.4 nM). Anandamide (1 microM) vasodilates juxtamedullary afferent arterioles perfused in vitro; the vasodilation can be blocked by nitric oxide (NO) synthase inhibition with L-NAME (0.1 mM) or CB1 receptor antagonism with SR 141716A (1 microM), but not by indomethacin (10 microM). Anandamide (10 nM) stimulates CB1-receptor-mediated NO release from perfused renal arterial segments; a similar effect was seen in EC. Finally, anandamide (1 microM) produces a NO-mediated inhibition of KCl-stimulated [3H]norepinephrine release from sympathetic nerves on isolated renal arterial segments. Hence, an anandamide signaling system is present in the kidney, where it exerts significant vasorelaxant and neuromodulatory effects.

L9 ANSWER 14 OF 16 MEDLINE on STN
AN 97017921 MEDLINE
DN 97017921 PubMed ID: 8864538
TI Inhibition of exocytotic noradrenaline release by presynaptic **cannabinoid** CB1 receptors on peripheral sympathetic nerves.
AU Ishac E J; Jiang L; Lake K D; Varga K; Abood M E; Kunos G
CS Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298, USA.
NC DA-07027 (NIDA)
HL 49938 (NHLBI)
SO BRITISH JOURNAL OF PHARMACOLOGY, (1996 Aug) 118 (8) 2023-8.
Journal code: 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970106
AB 1. Activation of CB1 receptors by plant cannabinoids or the endogenous ligand, anandamide, causes hypotension via a sympathoinhibitory action in anaesthetized rats. In mouse isolated vas deferens, activation of CB1 receptors inhibits the electrically evoked twitch response. To determine if these effects are related to presynaptic inhibition of noradrenaline (NA) release, we examined the effects of delta 9-tetrahydrocannabinol (delta 9-THC), anandamide and the CB1 antagonist, SR141716A, on exocytotic NA release in rat isolated atria and vasa deferentia. 2. In isolated atria and vasa deferentia preloaded with [3H]-NA, electrical field stimulation caused [3H]-NA release, which was abolished by tetrodotoxin 0.5 microM and concentration-dependently inhibited by delta 9-THC or

anandamide, 0.3-10 microM. The inhibitory effect of delta 9-THC and anandamide was competitively antagonized by SR 141716A, 1-10 microM. 3. Tyramine, 1 microM, also induced [3H]-NA release, which was unaffected by tetrodotoxin, delta 9-THC or anandamide in either atria or vasa deferentia. 4. CB1 receptor mRNA is present in the superior cervical ganglion, as well as in whole brain, cerebellum, hypothalamus, spleen, and vas deferens and absent in medulla oblongata and atria, as demonstrated by reverse transcription-polymerase chain reaction. There was no evidence of the presence of CB1A receptor mRNA in ganglia, brain, or cerebellum. These results suggest that activation of presynaptic CB1 receptors located on peripheral sympathetic nerve terminals mediate sympathoinhibitory effects in vitro and in vivo.

L9 ANSWER 15 OF 16 MEDLINE on STN DUPLICATE 2
AN 97000842 MEDLINE
DN 97000842 PubMed ID: 8843898
TI Mechanism of the hypotensive action of anandamide in anesthetized rats.
AU Varga K; Lake K D; Huangfu D; Guyenet P G; Kunos G
CS Department of Pharmacology and Toxicology, Virginia, Commonwealth University, Medical College of Virginia, Richmond 23298, USA.. kvarga@gems.vcu.edu
NC DA-07027 (NIDA)
HL-28785 (NHLBI)
HL-49938 (NHLBI)
SO HYPERTENSION, (1996 Oct) 28 (4) 682-6.
Journal code: 7906255. ISSN: 0194-911X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199611
ED Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961107
AB We studied the effects of the endogenous **cannabinoid** ligand anandamide on blood pressure, single unit activity of barosensitive neurons in the rostral ventrolateral medulla, and postganglionic splanchnic sympathetic nerve discharge in urethane-anesthetized rats. In rats with an intact baroreflex, an intravenous bolus of 4 mg/kg anandamide caused a triphasic blood pressure response: transient hypotension, followed by a brief pressor and more prolonged depressor phase. Anandamide evoked a "primary" increase in neuronal firing coincident with its pressor effect and a "secondary," baroreflex-mediated rise coincident with its depressor effect at both sites. Pretreatment of rats with phentolamine or trimethaphan did not inhibit either the pressor response or the primary increase in splanchnic nerve discharge elicited by anandamide. In barodenervated rats, electrical stimulation of the rostral ventrolateral medulla increased blood pressure and splanchnic nerve discharge. Anandamide treatment blunted the rise in blood pressure without affecting the increase in splanchnic nerve discharge. Anandamide did not affect the rise in blood pressure in response to an intravenous bolus dose of phenylephrine. The results indicate that (1) the brief pressor response to anandamide is not sympathetically mediated, and (2) the prolonged hypotensive response to anandamide is not initiated in the central nervous system, in ganglia, or at postsynaptic adrenergic receptors but is due to a presynaptic action that inhibits norepinephrine release from sympathetic nerve terminals in the heart and vasculature.

L9 ANSWER 16 OF 16 MEDLINE on STN DUPLICATE 3
AN 96082257 MEDLINE
DN 96082257 PubMed ID: 7589169
TI Novel antagonist implicates the CB1 **cannabinoid** receptor in the

hypotensive action of anandamide.

AU Varga K; Lake K; Martin B R; Kunos G
CS Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298-0613, USA.

NC HL49938 (NHLBI)
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (1995 May 24) 278 (3) 279-83.
Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
ED Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951212

AB In anaesthetised rats, the endogenous **cannabinoid** anandamide has potent cardiovascular effects that include a brief pressor effect and a more prolonged depressor response. The depressor response is attenuated after transection of the cervical spinal cord or blockade of alpha-adrenergic receptors by phentolamine, and is dose-dependently inhibited by a selective antagonist of the CB1 **cannabinoid** receptor. The pressor component is not affected by any of these interventions. This suggests that the depressor response is due to inhibition of sympathetic tone mediated by CB1 receptors, whereas the pressor component is due to a peripheral action that does not involve the same receptors or the **sympathetic nervous system**.

MARINOL® (dronabinol) Capsules 2.5 mg, 5 mg, 10 mg

Physician Information

Clinical Studies—AIDS

In this section:

6-Week Study[1]

In AIDS patients with anorexia associated with **weight loss**

Significant Appetite Improvement After 4 Weeks of Therapy

Study
Beal JE, et al. Dronabinol as a treatment for anorexia associated with **weight loss** in patients with AIDS. *J Pain Symptom Manage.* 1995;10(2):89-97.

Study Objective

- To evaluate the effects of **MARINOL®** (dronabinol) on appetite, **weight**, mood, and nausea

Study Participants

- 139 patients with AIDS-related anorexia and ≥ 2.3 kg **weight loss**

Study Design

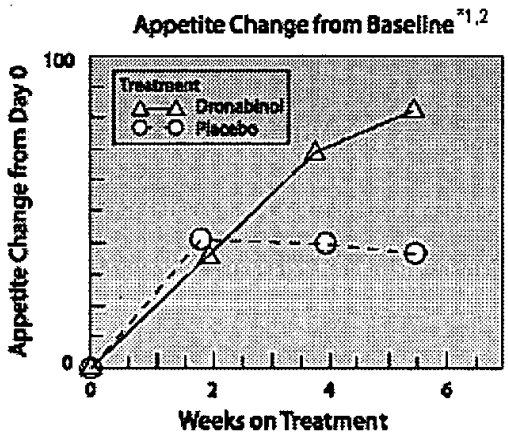
- Multicenter, double-blind, placebo-controlled, parallel-group study
- Patients were randomized to receive 2.5 mg dronabinol twice daily or placebo
- Duration was 6 weeks, encompassing a baseline visit and three biweekly follow-up evaluations
- Patients rated appetite, mood, and nausea using a 100-mm visual analogue scale 3 days weekly
- Change in **weight** was also measured

Study Results

- Efficacy was evaluable in 88 patients (50 of 72 dronabinol patients and 38 of 67 placebo patients)
- Dronabinol was associated with a statistically significant increase in

appetite above baseline (dronabinol 38%, placebo 8%, P=0.015 for evaluable patients at 6-week endpoint)
- Trends toward **weight** gain, improved mood, and decreased nausea were seen with dronabinol
- Significantly more patients taking dronabinol experienced treatment-related adverse events. These adverse events were mostly mild to moderate in severity (euphoria, dizziness, and thinking abnormalities)
- The majority of side effects reported were central nervous system disturbances commonly associated with cannabinoids
- There was no significant difference in patient dropout rates (dronabinol 8.3%, placebo 4.5%, P=0.29)

In the Treatment of Anorexia Associated With Weight Loss Due to AIDS



* Six-week results from a randomized, double-blind, placebo-controlled study of 139 patients.

Study Conclusion

- **MARINOL®** (dronabinol) is a safe and effective treatment for anorexia in patients with **weight loss** due to AIDS

Important Notes

- Based primarily on this study, the FDA approved dronabinol for the treatment of anorexia associated with **weight loss** in AIDS patients
- Dronabinol is the first drug to receive this indication

Precautions

- **MARINOL®** should be used with caution in patients with cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia
- **MARINOL®** should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence, because they may be more prone to abuse **MARINOL®** as well. Multiple substance abuse is common and marijuana, which contains the same active compound, is a frequently abused substance
- **MARINOL®** should be used with caution and careful psychiatric monitoring in patients with mania, depression, or schizophrenia because **MARINOL®** may exacerbate these illnesses
- **MARINOL®** should be used with caution in patients receiving concomitant therapy with sedatives, hypnotics, or other psychoactive drugs because of the potential for additive or synergistic CNS effects
- Although no drug/drug interactions were discovered during clinical trials of **MARINOL®**, cannabinoids may interact with other medications

Adverse Events

- The most frequently reported adverse experiences in patients with AIDS during placebo-controlled clinical trials involved the CNS and were reported by 33% of patients receiving **MARINOL®**. About 25% of patients reported a minor CNS adverse event during the first 2 weeks and about 4% reported such an event each week for the next 6 weeks.

Next: 12-Month Study

Physician Information • Patient Information • Patient Assistance Program • Prescribing Information

GMHC GAY MEN'S HEALTH CRISIS

Other Issues

HIV-related Weight Loss and Wasting

Gay Men's Health Crisis "Treatment Issues", Vol. 8, No. 8 - September 1994
David Pieribone

HIV-associated weight loss, or wasting syndrome, is a major cause of illness and death in patients with late-stage HIV infection. It can be divided into two categories: acute weight loss, which often rebounds after an opportunistic infection is brought under control, and chronic weight loss, which is more difficult to reverse. Either decreased nutrient intake or alterations in metabolism can lead to weight loss. These factors can arise directly from HIV infection as well as from opportunistic infections, cancers or pre-existing gastrointestinal disease.

It is important to differentiate between mere loss in weight and the loss of protein stores (in lean tissue) that occurs during HIV infection. When acute weight loss is halted by treating an opportunistic infection, an individual may regain lost weight by adding fat rather than rebuilding lean tissue. Simply taking in more nutrients does not automatically produce recovery from wasting. AIDS-related wasting differs qualitatively from starvation. In starvation, the body's protein stores and muscle mass is conserved while basic metabolic rates slow and fat deposits are broken down for energy. During AIDS, the reverse happens. Studies by Kotler and others meanwhile indicate that death from wasting is related to the loss of lean body mass rather than just the amount of weight loss.[1]

Alterations in Metabolism

Primary infection with HIV or secondary opportunistic infections changes the body's metabolic pathways. Abnormal patterns of protein and lipid metabolism result, with nutrients transferred from lean to adipose (fat) tissue. Some inflammatory cytokines (intercellular immune regulators), such as tumor necrosis factor (TNF) and interleukin-1, have been associated with metabolic dysregulation and wasting.[2] Their chronic release during HIV infection seems to play a major role in HIV-related wasting. Endocrine abnormalities, including changes in gonadal, adrenal and thyroid function, have been noted in HIV-infected individuals and are another possible cause of weight loss and wasting.[3,4] One recent paper reported that people with AIDS-related wasting syndrome had significantly less testosterone and more prolactin and cortisol than similar people without wasting.[5] Testosterone promotes the growth and maintenance of muscle tissue. The decrease in testosterone may be related to the increased prolactin. Cortisol is an adrenal hormone that modulates stress. One of its functions is to free existing protein stores to repair tissue damage elsewhere in the body. Finally, progressive muscle weakness (myopathy), is an ill-defined condition that may be caused by HIV itself or extended use of AZT. It is reversible in the latter case.

Approved Treatments for Wasting

Two appetite stimulants are the only FDA-approved therapies specifically for AIDS-related wasting syndrome.

Dronabinol (Marinol) is the psychoactive component of marijuana. In trials, dronabinol improved appetite and weight gain (mostly body fat) in about half of the participants. Side effects associated with Dronabinol include dizziness, thinking abnormalities, asthenia (weakness or loss of strength) and euphoria.

Megestrol acetate (Megace) is a synthetic progesterone (steroid hormone) in oral suspension. A twelve-week, placebo-controlled study conducted in patients with AIDS-related wasting provided the basis for its approval. Weight gains of five to seven pounds were observed in the megestrol acetate group, and two-pound losses were observed in the placebo group.[6] Phase II studies are underway to evaluate the combination of Marinol and Megace.

Side effects of Megace include high blood pressure, leg swelling, diabetes and impotence. (In addition, there was a trend toward a higher death rate in one study's treatment arm.) Megace, like Marinol, is widely considered to increase weight without adding to lean body mass (see article on the Tenth International Conference on AIDS). Appetite stimulants alone may not be able to overcome the basic metabolic changes wrought by the chronic response to HIV and the concurrent opportunistic infections. Reversing wasting may require "anabolic" agents that, like testosterone, promote muscle formation and discourage fat buildup.

Human Growth Hormone

Recombinant human growth hormone (rHGH) and insulin-like growth factor (IGF-1) are two growth stimulators currently under study as therapies for wasting.

rHGH is a synthetic version of pituitary gland-derived human growth hormone. It is made by genetic engineering and used for the treatment of dwarfism. rHGH can induce positive nitrogen balance, promote protein sparing and increase weight gain and lean body mass in patients with AIDS-related wasting.[7] Side effects of rHGH include joint aches, fevers and high blood pressure.

Two preliminary studies published last year found that human growth hormone triggered significant weight gain in people with HIV wasting.[8,9] See the box on the International Conference on AIDS for the first analysis of a much larger, more extended trial of rHGH. The presentation on this trial was very encouraging.

IGF-1 is produced by the liver in response to human growth hormone. Many, but not all, of growth hormone's effects seem to really be the result of IGF-1. A trial comparing growth hormone and insulin-like growth factor is being conducted at the National Cancer Institute, but a trial examining the combination of the two yielded negative results (see below).

Anabolic Steroids

Testosterone and the chemically similar synthetic anabolic steroids have been used by athletes and body builders to increase their muscle mass and stamina. Anabolic steroids can be dangerous, though, and medical supervision is desirable.

Community doctors have found that testosterone replacement therapy can improve patients' mood, sexual function, appetite and energy, although the long-term effects on immune function are not known. Testosterone replacement is generally not sufficient to manage weight loss and increasing testosterone levels to above normal can have adverse effects, including liver damage. A limited number of studies indicates that some of the newer synthetic oral testosterone derivatives have fewer side effects, and anecdotal reports claim that they increase immune cell populations (CD8 and CD4). Dr. Kotler, at St. Luke's/Roosevelt Hospital in New York, is conducting trials with oral oxandrolone, a synthetic anabolic. Early results indicate that patients taking oxandrolone experience weight gain. Upon termination of treatment, weight loss resumed, however. There was no evidence of CD8 or CD4 cell increases resulting from oxandrolone therapy. During short-term use, no overt side effects were noted but studies examining long- term use have not been done. The effects of anabolic steroids on women in particular need further monitoring, although oxandrolone is reputed to have few masculinizing effects.

Anabolic steroids such as deca-durabolin have become popular as an underground therapy among people with AIDS. Many feel that these compounds work much better when accompanied by a rigorous exercise program. Future studies should be conducted to evaluate the combination of anabolic steroids with growth hormone and testosterone replacement. The ideal therapy may well be an individualized one that includes hormone- and cytokine-modulating agents as needed but starts with such simple supportive measures as exercise and food supplements.

Cytokine Modulators

Pentoxifylline is a medication for blood circulation disorders. It also inhibits the activity of TNF and might in this way help reverse wasting syndrome. An NIH-sponsored study has found that after eight weeks on pentoxifylline, triglycerides (lipids) in blood serum dropped significantly and TNF production went down.[10] Researchers at the Veterans Affairs Hospital in Brooklyn, New York studied the drug's effect on wasting syndrome in patients with AIDS but were not able to detect any weight gain or reversal of wasting.[11] Another recent study found that pentoxifylline at a dose of 800 mg three times daily did not affect the T-cell counts, viral load or TNF in eight patients treated for three weeks.[12]

Thalidomide is enjoying a revival as a TNF blocker. Recently, two separate studies, one in France and another at Rockefeller University in New York City, have shown significant weight gain in patients receiving thalidomide. Thalidomide's abilities in this area are now the subject of further study. For the latest results, see the article on the AIDS Conference.

OP-1, a mixture of polypeptides, glycopeptides and glycosides, is another reputed TNF inhibitor. Its developer, Omega Pharmaceuticals, is just now beginning clinical trials of OP-1 for AIDS-related wasting.

Malabsorption

Cells in the GI tract are particularly prone to damage during HIV infection, and this results in reduced absorption of nutrients. The HIV virus itself, intestinal parasites, and colitis induced by cytomegalovirus (CMV) are the main sources of tissue damage. The diarrhea connected with these conditions also may result in malabsorption. Fat, carbohydrate, protein and micronutrient (vitamin and mineral) malabsorption can occur. Malabsorption may also be a condition that pre-exists infection with HIV.

Infection by intestinal parasites triggers diarrhea and malabsorption in persons with AIDS by causing atrophy of the villi - the small threadlike projections on the interior of the small intestines which absorb nutrients when working properly. Given the variety of intestinal parasites, electron microscopic analysis of intestinal biopsy is required for a conclusive diagnosis. This procedure is both uncomfortable and expensive. It is also difficult to perform and may be unavailable in many places.

The protozoa Cryptosporidium parvum, the most commonly identified parasite in people with AIDS, causes massive secretory diarrhea. Paramomycin (Humatin) at 500 mg four times a day has demonstrated positive results in some patients although relapse is common after the drug is discontinued.[14] For persons with a more mild infection, a lactose-free, low-fat diet with a high calorie, protein-rich fluid supplementation is helpful. The large amounts of sugars or long-chain proteins found in some nutritional drinks tend to engender bloating and heightened diarrhea. Persons with severe untreatable diarrhea may also require parenteral (intravenous) fluid administration to maintain a normal state of hydration and electrolyte balance.

Among the drugs under investigation for cryptosporidiosis is intravenous azithromycin. This formulation of the drug is available directly from the manufacturer, Pfizer, on a compassionate use basis (call 800/742-3029 for further information). Side effects of IV azithromycin include nausea and abdominal pain. Oral azithromycin failed to show an effect on the frequency of bowel movements, parasite shedding in the stool or overall clinical response in a placebo-controlled study of 90 patients with cryptosporidiosis conducted at Cornell Medical Center.[15]

Another anti-crypto agent in development consists of concentrated antibodies derived from cow's milk. Bioimmune Systems of Salt Lake City is just beginning preliminary human trials in HIV-negative individuals of its oral, milk-derived antibody product, known as Immuno-C. An efficacy trial for 40 people with AIDS-related cryptosporidiosis is expected later in the fall and will include six to eight sites around the country. More information may be obtained by calling Joy Erickson of Bioimmune Systems at 801/582-2345.

A second cow's milk preparation is called CryptoGAM. It is manufactured by Immucell and licensed by Univax. CryptoGAM failed as an oral agent in several early trials apparently because it was broken down in the stomach before it reached the intestines. A new open label trial is currently being conducted by Louis Fries, M.D., from Univax. Very high dose CryptoGAM (40 grams per day) is introduced directly into the duodenum via a nasogastric tube. Patients interested in the trial can contact Dr. Fries at 301/770- 3099.

Microsporidia (Enterocytozoon bieneusi or Septata intestinalis) is a second common GI parasite in people with AIDS. Infection can cause diarrhea and decreased intestinal absorption.[16] The drug albendazole has shown some promise and is currently the subject of an NIH- sponsored trial. A preliminary report on eight patients from Dr. Dominique Anwar of Grady Memorial Hospital in Atlanta indicates that atovaquone (an approved treatment for pneumocystis pneumonia) may be effective in reducing diarrhea.[17]

As a preventive measure, HIV-infected people with low CD4 counts should be extremely careful about the water they consume. There are only three acceptable forms: distilled, deionized or boiled. Water filters, standing water (wells), spa waters and bottled spring water can be contaminated with intestinal parasites. Ice cubes and soda fountain-type drinks which mix tap water with syrup can also be contaminated. Use distilled, deionized or boiled water in all foods that will not be cooked and require water for their preparation. Because even the smallest amount of contaminated water can cause infection, fruits and vegetables rinsed with tap water could be a source of parasistes.

Nutritional Support

Nutritional support is very important for individuals with HIV infection. Anabolic drugs will have little effect without sufficient diet. Studies also indicate that diets high in protein and complex carbohydrates, moderate in fats and sugars are important for good immune function.

Use of nutritional drinks such as Nutren, Ensure Plus, and Sustacal can increase caloric intake for individuals who are having trouble consuming enough calories. Because both individuals' needs and the products' compositions vary, one supplement may be better suited than another for a particular situation. Patients should consult their physicians or a nutritional counselor before adding nutritional drinks to their diets. Little data from controlled trials exist, though, so it is difficult to assess the actual benefit of supplementation. Lipisorb is a food supplement containing medium chain triglycerides that may benefit patients with fat malabsorption. Elemental (predigested) diets are comparatively easy to absorb in the GI tract and reportedly have helped lessen diarrhea and stabilize weight.[18] In patients unable to eat, data from two studies suggest that enteral gastrostomy feeding (feeding through a tube placed directly into the stomach through the skin) can result in weight gain and increased lean body mass.[19]

Total parenteral nutrition (TPN) is a form of liquid nutrition infused directly into the bloodstream. Studies indicate that patients receiving TPN gain significant amounts of body cell mass and weight if they are free of systemic

infections. Other studies have shown that administering TPN during secondary infection can increase weight gain and improve the quality of life by improving the individual's ability to fight infection.[20] Investigators also have reported that TPN has favorable effects on immune cell responsiveness.[21] But TPN can cost up to $13,000 a month in a home care environment. It is usually used to support someone through a limited period of acute illness but may be required for more lengthy periods.

Exercise

Exercise can promote protein formation in tissues throughout the body. It is a helpful therapy when physical health permits. To build up lean body mass, resistance exercises (such as weight lifting) are more important than aerobic exercises, although aerobic exercise can also be beneficial. Exercise promotes muscle formation by increasing the number of testosterone receptors. Proper timing of food intake is also important in weight lifting. It is a good idea to eat well but not immediately prior to lifting weights and to eat a high protein food one to two hours after lifting.

Conclusion

A variety of therapeutic strategies are available for different aspects of HIV-associated wasting. There is a strong correlation between proper weight, good nutritional status and survival.[22] Individuals should chart their weight, noting any significant change, and physicians should take determined steps to diagnose and treat major weight loss. Correct diagnosis and aggressive treatment can improve quality of life and prolong survival.

1 Kotler DP et al. American Journal of Clinical Nutrition. Sept 1989; 50(12):444-7.

2 Lombard RP et al. Clinical Immunology and Immunopathology. 1989; 50:374-84.

3 Jones PD et al. Journal of Acquired Immune Deficiency Syndromes. Dec 1992; 5:1266-71.

4 Landman A et al. Thirty-second Interscience Conference on Antimicrobial Agents and Chemotherapy. Oct 1992; abstract 568.

5 Coodley GO et al. Journal of Acquired Immune Deficiency Syndromes. Jan 1994; 7(1):46-51.

6 Flynn N et al Eighth International Conference on AIDS Jul 1992; 8(2): B205. abstract PoB3687.

7 Grunfeld C et al. Eighth International Conference on AIDS Jul 1992; 8(2): B230. abstract PoB3835.

8 Krentz AJ et al. Journal of Acquired Immune Deficiency Syndromes. Mar 1993; 6(3):245-251.

9 Mulligan K et al. Journal of Clinical Endocrinology and Metabolism. Oct 1993; 77(4):956-62.

10 Dezube BJ et al. Journal of Acquired Immune Deficiency Syndromes. Jul 1993; 6(7): 787-94.

11 Landman A et al. Thirty-second Interscience Conference on Antimicrobial Agents and Chemotherapy. Oct 1992; abstract 568.

12 Mole L et al. Journal of Acquired Immune Deficiency Syndromes. May 1994; 7(5):520-1.

13 Lahdevirta J et al. American Journal of Medicine. Sept 1988; 85(3):289-91.

14 Armitage K et al. Archives of Internal Medicine. Dec 1992; 152(12):2497-9.

15 Soave R et al. Thirty-third Interscience Conference on Antimicrobial Agents and Chemotherapy. October 1993; abstract 405.

16 Hecker LM et al. Nutrition Reviews. Nov 1990; 48(11):393-401.

17 Torres G, personal communication.

18 Hickey MS. Surgical Clinics of North America. Jun 1991; 71(3):645-64.

19 Kotler DP et al. American Journal of Clinical Nutrition. 1991; 53(1):149-54.

20 Campelli A et al Eighth International Conference on AIDS. Jul 1992; 8(2): 63.

21 Singer P et al. Journal of Parenteral and Enteral Nutrition. Jan- Feb 1991; 15(1):75-9.

22 Guenter P et al. Journal of Acquired Immunodeficiency Syndromes. Oct 1993; 6(10):1130-8.
